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ning of each regular issue of the PCT Gazette.*

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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING A HMG COA REDUCTASE INHIBITOR

(57) Abstract: The present invention relates to pharmaceutical compositions and more particularly to a pharmaceutical composition containing (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-{methyl(methylsulfonyl)amino}pyrimidin-5-yl]-(3R, 5S)-3,5-dihydroxy-hept-6-enoic acid or a pharmaceutically-acceptable salt thereof as the active ingredient and an inorganic salt in which the cation is multivalent.

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PHARMACEUTICAL COMPOSITIONS COMPRISING A HMG COA REDUCTASE INHIBITOR

The present invention relates to pharmaceutical compositions and more particularly to a pharmaceutical composition containing (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-
5 [methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R, 5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically-acceptable salt thereof (and referred to hereinafter as "the Agent"). In particular the sodium and calcium salts, and especially the calcium salt, bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R, 5S)-3,5-dihydroxyhept-6-enoic acid]calcium salt (shown as Formula I below).

10

The Agent is disclosed as an inhibitor of 3-hydroxy-3-methylglutaryl CoA reductase (HMG CoA reductase) in European Patent Application , Publication No. 0521471 and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444 and is useful in the treatment of hypercholesterolemia, hyperlipidproteinemia and atherosclerosis.

15

A problem associated with the Agent is that it is particularly sensitive to degradation under certain conditions. The major degradation products formed are the corresponding (3R, 5S) lactone (hereinafter referred to as "the lactone") and an oxidation product (hereinafter referred to as "B2") in which the hydroxy group adjacent to the carbon-carbon double bond is
20 oxidised to a ketone functionality. The potential for significant degradation of the Agent makes it difficult to formulate and provide a pharmaceutical composition with acceptable storage life for a marketed product.

Pharmaceutical formulations of certain 7-substituted-3,5-dihydroxy-6-heptenoic acid
25 salts, which are HMG CoA reductase inhibitors, are disclosed in UK Patent 2 262 229, and that they are sensitive to pH degradation. These formulations require the presence of an alkaline medium (such as a carbonate or bicarbonate) capable of imparting a pH of at least 8 to an aqueous solution or dispersion of the composition.

30 However, we have found that for the Agent it is not sufficient to improve stability by solely controlling pH in the formulation.. We have found that with the Agent stability is

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improved by selection of an inorganic salt to be added to the composition which contains one or more multivalent inorganic cations. Whilst not wishing to be bound by theory we believe that the multivalent inorganic cation stabilises the structure of the Agent and makes it less susceptible to oxidation and/or lactonization.

5

We present as a feature of the invention

(1) A pharmaceutical composition comprising the Agent as an active ingredient and an inorganic salt in which the cation is multivalent.

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(2) The use of an inorganic salt in which the cation is multivalent as a stabilising agent in a pharmaceutical composition comprising the Agent.

Preferred features of the invention are:

15

(1) wherein the Agent is present in the composition is more than 5mg, preferably more than 10mg. Excluded compositions are those wherein the Agent is present at 1mg, 2mg, 5mg and 10mg. Preferred compositions are those where the amount of Agent is 20mg, 40mg or 80mg.

20

(2) wherein the stabilising compound is not synthetic hydrotalcite.

(3) the pharmaceutical composition formed is a tablet or a powder.

25

Preferably the pharmaceutical composition of the invention is a tablet.

The multivalent cation found in the inorganic salt may be selected from the following, calcium, magnesium, zinc, aluminium and iron or a mixture thereof. Preferred multivalent cations are calcium, aluminium and magnesium or a mixture thereof. Especially preferred

30 multivalent cations are aluminium and magnesium or a mixture thereof.

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The counter anion in the inorganic salt may be selected from a phosphate, a carbonate, a silicate, an oxide and a metasilicate. Preferred counter anions are selected from a carbonate, a silicate, an oxide and a metasilicate. Especially preferred counter anions are selected from a silicate, an oxide or a metasilicate.

5

Individual aspects of the invention include an inorganic salt comprising a multivalent cation selected from any of the above and a counter anion also selected from any of the above.

Preferred inorganic salts for use in the present invention are; aluminium magnesium
10 metasilicate (Neusolin™, Fuji Chemical Industry Limited), dibasic or tribasic calcium phosphate, tribasic magnesium phosphate and tribasic aluminium phosphate. Aluminium magnesium metasilicate and tribasic calcium phosphate are especially preferred.

It is also preferable that such a composition has a good flow rate to assist processing
15 into unit dosage forms for oral administration, for example into tablets, and good disintegration and dissolution characteristics when processed into tablets for oral administration, which tablets can be in different dosage strengths.

The ratio of inorganic salt to Agent in the pharmaceutical composition is, for example,
20 within the range of 1:80 to 50:1 by weight, for example 1:50 to 50:1 by weight, such as 1:10 to 10:1 by weight, and more particularly 1:5 to 10:1 by weight.

Preferably the pharmaceutical composition of the invention is formulated into an oral dosage form, such as a tablet. Accordingly a further aspect of the invention comprises a
25 pharmaceutical composition comprising the Agent, an inorganic salt in which the cation is multivalent, and one or more fillers, binders, disintegrants or lubricants. A still further aspect of the invention relates to a pharmaceutical composition for oral administration comprising the Agent, one or more fillers, one or more binders, one or more disintegrants, one or more lubricants and an inorganic salt in which the cation is multivalent.

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Suitable fillers include, for example, lactose, sugar, starches, modified starches, mannitol, sorbitol, inorganic salts, cellulose derivatives (e.g. microcrystalline cellulose, cellulose), calcium sulfate, xylitol and lactitol.

5 Suitable binders include, for example, polyvinylpyrrolidone, lactose, starches, modified starches, sugars, gum acacia, gum tragacanth, guar gum, pectin, wax binders, microcrystalline cellulose, methylcellulose, carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, copolyvidone, gelatin and sodium alginate.

10

Suitable disintegrants include, for example, crosscarmellose sodium, crospovidone, polyvinylpyrrolidone, sodium starch glycollate, corn starch, microcrystalline cellulose, hydroxypropyl methylcellulose and hydroxypropyl cellulose.

15 Suitable lubricants include, for example, magnesium stearate, stearic acid, palmitic acid, calcium stearate, talc, carnauba wax, hydrogenated vegetable oils, mineral oil, polyethylene glycols and sodium stearyl fumarate.

Additional conventional excipients which may be added include preservatives,
20 stabilisers, anti-oxidants, silica flow conditioners, antiadherents or glidants.

Other suitable fillers, binders, disintegrants, lubricants and additional excipients which may be used are described in *Handbook of Pharmaceutical Excipients*, 2nd Edition, American Pharmaceutical Association; *The Theory and Practice of Industrial Pharmacy*, 2nd Edition,
25 Lachman, Leon, 1976; *Pharmaceutical Dosage Forms: Tablets Volume 1*, 2nd Edition, Lieberman, Hebert A., et al, 1989; *Modern Pharmaceutics*, Banker, Gilbert and Rhodes, Christopher T, 1979; and *Remington's Pharmaceutical Sciences*, 15th Edition, 1975.

Typically the Agent will be present in an amount within the range of 1 to 50%, for
30 example 1 to 25%, such as 1 to 20%, and particularly 5 to 18% by weight.

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Typically the inorganic salt, such as tribasic calcium phosphate, will be present in an amount within the range of 1 to 25%, for example 1 to 20%, such as 5 to 18% by weight.

Typically one or more fillers will be present in an amount 30 to 90% by weight.

5

Typically one or more binders will be present in an amount 2 to 90% by weight.

Typically one or more disintegrants will be present in an amount 2 to 10%, and especially 4 to 6% by weight.

10

It will be appreciated that a particular excipient may act as both a binder and a filler, or as a binder, a filler and a disintegrant. Typically the combined amount of filler, binder and disintegrant comprises, for example, 70 to 90% by weight of the composition.

15

Typically one or more lubricants will be present in an amount 0.5 to 3%, and especially 1 to 2% by weight.

The pharmaceutical composition of the invention may be prepared, using standard techniques and manufacturing processes generally known in the art, for example by dry
20 blending the components. For example, the Agent and an inorganic salt in which the cation is multivalent, one or more fillers, one or more binders and one or more disintegrants, as well as other additional excipients if desired are blended together. The components of the blend prior to blending, or the blend itself, may be passed through a mesh screen, for example a 400-700 μm mesh screen. A lubricant, which may also be screened, is then added to the blend and
25 blending continued until a homogeneous mixture is obtained. The mixture is then compressed into tablets. Alternatively, a wet granulation technique can be employed. For example, the Agent and an inorganic salt in which the cation is multivalent, one or more fillers, one or more binders and a portion of a disintegrant, as well as other additional excipients if desired, are blended together, for example by using a granulator, and the powder blend is granulated
30 with a small volume of purified water. The granulate is dried and passed through a mill. The remainder of the disintegrant and a lubricant are added to the milled granulation and after

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blending the resultant homogeneous mixture is compressed into tablets. It will be appreciated that modifications of the dry blending and wet granulation techniques, including the order of addition of the components and their screening and blending prior to compression into tablets, may be carried out according to principles well known in the art.

5

A tablet coating may then be applied, for example by spray-coating, with a water-based film coating formulation. The coating may comprise, for example, lactose, hydroxypropyl methylcellulose, triacetin, titanium dioxide and ferric oxides. Coating ingredient combinations are commercially available, such as those described in the Examples hereinafter. The coating may comprise, for example, 0.5 to 10% by weight of the tablet composition, particularly 1 to 6%, and preferably 2 to 3%. Coatings containing ferric oxides are especially preferred as they reduce the rate of formation of photodegradation products of the Agent.

15 Accordingly we present as a feature of the invention a pharmaceutical composition comprising the Agent, the composition having a ferric oxide light protective coating.

A further aspect of the present invention comprises a method of preparing a stabilised pharmaceutical composition which comprises admixing the Agent with an inorganic salt in which the cation is multivalent. A further aspect of the present invention comprises a method of producing a stabilised pharmaceutical composition which comprises incorporating a inorganic salt in which the cation is multivalent in a pharmaceutical composition containing the Agent.

25 **Example 1**

The Agent	2.50 mg
Tribasic calcium phosphate	20.0 mg
Microcrystalline cellulose	47.0 mg
30 Lactose monohydrate	47.0 mg
Sodium starch glycollate	3.00 mg

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Butylated hydroxytoluene	0.05 mg
Magnesium stearate	1.00 mg

The Agent, microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, tribasic calcium phosphate, and butylated hydroxytoluene were blended together for 10 minutes. Magnesium stearate was screened through a #40 mesh (425 μ m) screen and added to the blend and blending continued for a further three minutes. The resulting homogeneous mixture was compressed into tablets.

The tablets were stored at 70°C/80% relative humidity for one week. After one week there was found to be only 0.11%w/w of the oxidation product B2 formed and only 0.50%w/w of the lactone.

Example 2

15

The Agent	2.50 mg
Povidone	2.50 mg
Tribasic calcium phosphate	20.0 mg
Microcrystalline cellulose	47.0 mg
20 Mannitol	47.0 mg
Sodium starch glycolate	3.00 mg
Butylated hydroxytoluene	0.05 mg
Magnesium stearate	1.00 mg

The Agent, povidone, mannitol, microcrystalline cellulose, butylated hydroxytoluene, tribasic calcium phosphate and sodium starch glycolate (in the amounts given below) were blended for 5 to 60 minutes. Magnesium stearate was screened through a #40 mesh (425 μ m) screen and added to the blend and blending continued for a further three minutes. The resulting homogeneous mixture was compressed into tablets. The compressed tablets were coated by spraying with a mixture of hydroxypropyl methylcellulose, polyethylene glycol 400, titanium dioxide and ferric oxide (sold as Spectrablend™ by Warner-Jenkinson)) and

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water in a coating pan. The weight gain provided by the coating was 1 to 6%w/w, and preferably 2 to 3 %w/w.

The tablets were stored at 70°C/80% relative humidity for one week. After one week
5 there was found to be only 0.06%w/w of the oxidation product B2 formed and only 2.22%w/w of the lactone.

Example 3

10	The Agent	2.60 mg
	Crospovidone	3.75 mg
	Tribasic calcium phosphate	5.66 mg
	Microcrystalline cellulose	15.5 mg
	Lactose monohydrate	46.5 mg
15	Magnesium stearate	0.94 mg

The Agent and crospovidone were blended together for 5 minutes and the blend then passed through a 400-700µm screen. A small portion of the microcrystalline cellulose was passed through the screen afterwards. The screened material was blended with the other
20 ingredients, excluding the lubricant, for 10 minutes. Magnesium stearate was passed through a #40 mesh (425 µm) screen and added to the blend and the mixture was blended for a further 3 minutes. The resulting homogeneous mixture was compressed into tablets. The compressed tablets were coated by spraying with a mixture of lactose monohydrate, hydroxypropyl methylcellulose, triacetin and ferric oxide (sold as Opadry II™ by Colorcon)
25 and water in a coating pan. The weight gain provided by the coating is 1 to 6%w/w, and preferably 2 to 3%w/w.

The tablets were stored at 70°C/80% relative humidity for one week. After this time only 0.19%w/w of the oxidation product B2 had formed and only 2.71%w/w of the lactone.

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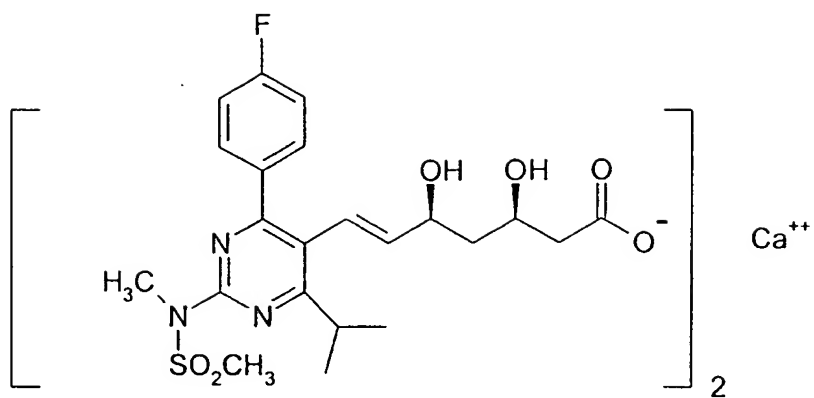
Example 4

	The Agent	2.50 mg
	Povidone	2.50 mg
5	Tribasic calcium phosphate	20.0 mg
	Microcrystalline cellulose	34.5 mg
	Lactose monohydrate	34.0 mg
	Sodium starch glycollate	6.00 mg
	Magnesium stearate	1.00 mg
10	Butylated hydroxytoluene	0.05 mg

A portion of the tribasic calcium phosphate and butylated hydroxytoluene were blended for 30 seconds in a bag. The Agent, povidone, remainder of the tribasic calcium phosphate, microcrystalline cellulose, lactose monohydrate, tribasic calcium
15 phosphate/butylated hydroxytoluene mixture and a portion of the sodium starch glycolate were blended in a granulator for 30 seconds. The powder blend was granulated with purified water for 1 minute at the addition rate of 70 mg/tablet/minute. The granulation is dried in a fluidized bed drier at 50°C until the loss on drying is less than 2% w/w. The dried granulation is passed through a mill (e.g. Comil™). The milled granulation and the remainder of the
20 sodium starch glycolate was blended for approximately 5 minutes. Magnesium stearate was screened through a #40 mesh (425 µm) screen and added to the blend and blending continued for a further three minutes. The resulting homogeneous mixture was compressed into tablets.

The tablets were stored at 70°C/80% relative humidity for one week. After this time
25 only 0.23 %w/w of the oxidation product B2 had formed and only 0.28%w/w of the lactone.

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Formula I

CLAIMS

1. A pharmaceutical composition comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R, 5S)-3,5-dihydroxyhept-6-enoic acid or a
5 pharmaceutically acceptable salt thereof as the active ingredient and an inorganic salt in which the cation is multivalent.
2. A pharmaceutical composition as claimed in claim 1 wherein the cation of the inorganic salt is selected from calcium, magnesium, zinc, aluminium and iron.
- 10 3. A pharmaceutical composition as claimed in claim 1 wherein the inorganic salt is selected from aluminium magnesium metasilicate, tribasic calcium phosphate, tribasic magnesium phosphate and tribasic aluminium phosphate.
- 15 4. A pharmaceutical composition as claimed in 3 wherein the inorganic salt is aluminium magnesium metasilicate.
5. A pharmaceutical composition as claimed in any of claims 1 to 4 which is a tablet or powder.
- 20 6. A pharmaceutical composition as claimed in any of claims 1 to 5 in which more than 5mg of active ingredient is present.
7. A pharmaceutical composition as claimed in any of claim 6 in which more than 10mg
25 of active ingredient is present.
8. A pharmaceutical composition as claimed in any of claims 1 to 7 wherein the inorganic salt in which the cation is multivalent is not synthetic hydrotalcite.
- 30 9. A pharmaceutical composition as claimed in any of claims 1 to 8 wherein the ratio of the inorganic salt to the active ingredient is in the range of 1:80 to 50:1 by weight.

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10. A pharmaceutical composition as claimed in any preceding claim additionally comprising one or more fillers, binders, disintegrants or lubricants.

5 11. A pharmaceutical composition as claimed in any of claims 1 to 6 wherein the active ingredient is present in an amount 1 to 50% by weight of the composition.

12. A pharmaceutical composition as claimed in any of claims 1 to 6 wherein the inorganic salt is present in an amount 1 to 50% by weight of the composition.

10

13. A pharmaceutical composition as claimed in claim 10 wherein the filler is present in an amount 30 to 90% by weight of the composition.

14. A pharmaceutical composition as claimed in claim 10 or 13 wherein the binder is
15 present in an amount 2 to 90% by weight of the composition.

15. A pharmaceutical composition as claimed in claim 10, 13 or 14 wherein the disintegrant is present in an amount 2 to 10% by weight of the composition.

20 16. A pharmaceutical composition as claimed in claim 10, 13, 14 or 15 wherein the lubricant is present in an amount 0.5 to 3% by weight.

17. A pharmaceutical composition as claimed in any preceding claim wherein the active ingredient is the calcium salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-
25 [methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R, 5S)-3,5-dihydroxyhept-6-enoic acid.

18. The use of an inorganic salt in which the cation is multivalent to stabilise the compound (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R, 5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof.

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19. Use as claimed in claim 18 wherein the inorganic salt in which the cation is multivalent is selected from aluminium magnesium metasilicate, tribasic calcium phosphate, tribasic magnesium phosphate and tribasic aluminium phosphate.
- 5 20. Use as claimed in claim 19 wherein the inorganic salt in which the cation is aluminium magnesium metasilicate.
21. A method of producing a stabilised pharmaceutical composition which comprises incorporating an inorganic salt in which the cation is multivalent in a pharmaceutical
- 10 composition containing the compound (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R, 5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof.
22. A method as claimed in claim 21 wherein the inorganic salt in which the cation is
- 15 multivalent is aluminium magnesium metasilicate.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 521 471 A (SHIONOGI & CO) 7 January 1993 (1993-01-07) cited in the application	1,2,6-9
Y	page 2, line 1 - line 29 page 4, line 18 - line 28 examples 1,7 claims 1,5-9	1-22
Y	GB 2 262 229 A (SANDOZ LTD) 16 June 1993 (1993-06-16) cited in the application page 1, paragraph 1 -page 2, paragraph 2 page 3, paragraph 2 -page 5, paragraph 1 page 6, paragraph 2 page 6, last paragraph -page 8, paragraph 1 example 1	1-22

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WO 97 23200 A (KOWA CO ;NISSAN CHEMICAL IND LTD (JP); MURAMATSU TOYOJIRO (JP); MA) 3 July 1997 (1997-07-03)</p> <p>page 1, line 27 -page 3, line 5</p> <p>page 3, line 15 - line 25</p> <p>page 5, line 3 -page 7, line 14</p> <p>examples 1,2,4</p> <p>claims</p> <p>----</p>	1-22
Y	<p>GRAUL A ET AL: "ZD-4522: Hypolipidemic HMG-CoA reductase inhibitor." DRUGS OF THE FUTURE, vol. 24, no. 5, May 1999 (1999-05), pages 511-513, XP000882032 ISSN: 0377-8282 the whole document</p> <p>----</p>	1-22
E	<p>WO 00 45817 A (PEARS JOHN STUART ;ASTRAZENECA UK LTD (GB); YAMAGUCHI YOSHITAKA (J) 10 August 2000 (2000-08-10)</p> <p>page 4, line 13 - line 16; figure 1</p> <p>page 37, line 20 -page 38, line 5</p> <p>----</p>	1,2, 5-17,21, 22
E	<p>WO 00 45818 A (CAMERON NORMAN EUGENE ;ASTRAZENECA UK LTD (GB); COTTER MARY ANNE () 10 August 2000 (2000-08-10)</p> <p>page 2, line 14 - line 17; figure 1</p> <p>examples 3,4</p> <p>----</p>	1,2, 5-17,21, 22
E	<p>WO 00 45819 A (RAZA ALI ;ASTRAZENECA UK LTD (GB)) 10 August 2000 (2000-08-10)</p> <p>page 11, line 10 - line 28</p> <p>claims 9-12</p> <p>-----</p>	1,2,5-7, 9-17,21, 22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/03017

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0521471 A	07-01-1993	CA 2072945 A	02-01-1993
		HU 61531 A	28-01-1993
		JP 2648897 B	03-09-1997
		JP 5178841 A	20-07-1993
		KR 9605951 B	06-05-1996
		US 5260440 A	09-11-1993
GB 2262229 A	16-06-1993	AT 401872 B	27-12-1996
		AT 190595 A	15-05-1996
		AT 401870 B	27-12-1996
		AT 244992 A	15-05-1996
		AU 661075 B	13-07-1995
		AU 3006992 A	17-06-1993
		CA 2085037 A	13-06-1993
		CH 684309 A	31-08-1994
		CZ 9203633 A	15-09-1993
		CY 1994 A	05-09-1997
		DE 4240430 A	17-06-1993
		EP 0547000 A	16-06-1993
		ES 2142819 T	01-05-2000
		FI 925615 A	13-06-1993
		FR 2684876 A	18-06-1993
		GR 3032929 T	31-07-2000
		HK 25597 A	06-03-1997
		HU 63328 A, B	30-08-1993
		IL 104041 A	27-12-1998
		IT 1256698 B	12-12-1995
		JP 2774037 B	09-07-1998
		JP 5246844 A	24-09-1993
		LU 88201 A	09-09-1994
		MX 9207152 A	01-07-1993
		NO 302099 B	26-01-1998
		NZ 245421 A	27-11-1995
		NZ 270729 A	27-11-1995
		PT 547000 T	30-06-2000
		RO 111542 A	29-11-1996
		RU 2121835 C	20-11-1998
		SK 363392 A	09-11-1994
		US 5356896 A	18-10-1994
		ZA 9209642 A	13-06-1994
WO 9723200 A	03-07-1997	AU 1171597 A	17-07-1997
		CA 2213608 A	03-07-1997
		CZ 9702681 A	13-05-1998
		EP 0814782 A	07-01-1998
		HU 9903536 A	28-03-2000
		JP 11503763 T	30-03-1999
		NO 973814 A	13-10-1997
		NZ 324446 A	30-08-1999
		PL 321868 A	22-12-1997
		RU 2142790 C	20-12-1999
		SK 116097 A	04-03-1998
WO 0045817 A	10-08-2000	NONE	
WO 0045818 A	10-08-2000	NONE	
WO 0045819 A	10-08-2000	NONE	